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Randomized Control Trials

Four-oil intravenous lipid emulsion effect on plasma fatty acid composition, inflammatory markers and clinical outcomes in acutely ill patients: A randomised control trial (Foil fact)

V. Donoghue [a, *], G.K. Schleicher [b], M.G.L. Spruyt [c], L. Malan [d], D.G. Nel [e], P.C. Calder [f], R. Blaauw [a]

[a] Division of Human Nutrition, Faculty of Medicine and Health Sciences, Stellenbosch University, Stellenbosch, South Africa
[b] Wits Donald Gordon Medical Centre ICU, Parktown, Johannesburg, South Africa
[c] Critical Care, Faculty of Health Sciences, University of the Free State, Bloemfontein, South Africa
[d] Centre of Excellence for Nutrition, North-West University, Potchefstroom Campus, South Africa
[e] Centre for Statistical Consultation, Stellenbosch University, Stellenbosch, South Africa
[f] Faculty of Medicine, University of Southampton, UK and NIHR Southampton Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust and University of Southampton, Southampton, UK

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SUMMARY

Background and aims: Data in critically ill patients on the effect of intravenous lipid emulsions (LEs), containing omega-3 polyunsaturated fatty acids (PUFAs), in parenteral nutrition (PN) are scarce and conflicting. This study compared the effects of a four-oil LE (30% soybean oil, 30% medium-chain triglycerides, 25% olive oil and 15% fish oil (FO)) (SMOFlipid®) to those of a 100% soybean oil-based LE in critically ill adult intensive care unit (ICU) patients.

Methods: In this double-blind, randomised study, patients (n = 75) predicted to need PN for more than 5 days were randomised to receive either a four-oil LE (Study Group (SG)) or a 100% soybean oil LE (Control Group (CG)). Isocaloric, isonitrogenous PN was administered continuously for 5 days. FO was provided at a dose of 0.09–0.22 g/kg body weight. Measurements included biochemical parameters and sequential organ failure assessment (SOFA) score daily and plasma total phospholipid fatty acids (FAs) and cytokine levels on days 1, 3, 6. Days on mechanical ventilation, length of stay and mortality were also recorded. ANOVA was used to compare response variables between the two groups over the time and Pearson correlation was used to measure relationships between continuous variables.

Results: 68 patients completed the study (n = 35 SG, n = 33 CG), with male predominance (66% SG, 56% CG). Average age was 60.8 ± 13.9 years (SG) versus 55.7 ± 14.8 (CG) (p = 0.143). The majority were surgical admissions (85% SG versus 91% CG) followed by medical. Plasma phospholipid oleic acid ($p = 0.022$) and alpha-linolenic acid ($p<0.0005$) increased in both groups. In the SG, plasma phospholipid EPA and DHA increased (both $p<0.001$), whereas the omega-6:omega-3 PUFA (n-6:n-3 PUFA) ratio decreased ($p < 0.001$). Aspartate aminotransferase (AST), alanine aminotransferase (ALT) and bilirubin decreased in both treatment groups. Considering only the change from day 1 to day 6 there was a bigger decrease in AST, ALT and bilirubin levels in the SG. Concentrations of TNF-α decreased from day 1 to day 6 in the SG, whereas they increased in the CG, but the change was not statistically significant ($p = 0.112$). A significant negative correlation was found between EPA provision on day 3 and the SOFA score ($r = -0.4047$, $p = 0.018$). Days on mechanical ventilation (1.24 ± 0.83 days in SG versus 0.88 ± 1.63 days in CG, $p = 0.385$) and ICU LOS (9.5 ± 7.09 days in SG versus 10.7 ± 7.6 days in CG, $p = 0.490$) were not different between groups.

Conclusion: PN containing a four-oil LE increased plasma EPA and DHA, decreased n-6:n-3 PUFA ratio, and was safe and well tolerated. The negative relationship between day 3 EPA and SOFA score seems promising, but EPA intake and effects may have been diluted by enteral nutrition which was started in more than half of patients on day 4. There was no significant difference in terms of other biochemical

* Corresponding author: Veronique Donoghue. P.O Box 3279, Parklands, Johannesburg, 2193, South Africa.
E-mail address: veronique.donoghue@gmail.com (V. Donoghue).

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measurements, SOFA score, length of ICU stay and mortality. More research is needed in this patient population, particularly regarding dose, duration and timing of FO and the effects on clinical outcomes.

1. Introduction

Critical illness is a multisystem process that can result in significant morbidity and mortality. In most patients, critical illness is preceded by a physiological deterioration, characterised by a catabolic state and intense metabolic changes, resulting in malnutrition and impaired immune functions [1].

Sepsis remains a common problem in critically ill patients. The prevalence of the systemic inflammatory response syndrome (SIRS) is estimated to range from 20% to 60%. Approximately 40% of patients with sepsis may develop septic shock [2]. Severe sepsis and septic shock have high mortality rates and are the leading causes of death in intensive care units [3]. There is an increasing awareness that patients who survive sepsis often have long-term physical, psychological and cognitive disabilities with significant health care and social implications [4].

Intravenous lipid emulsions (IVLEs) constitute the main source of energy and fatty acids (FAs) in parenteral nutrition (PN) formulations. However, they can be associated with the development of adverse effects [5]. FAs play key roles in determining the structural integrity and fluidity of cell membranes and can give rise to many important bioactive mediators. They can also regulate the expression of a variety of genes and modulate cell-signalling pathways, such as those involved in apoptosis, inflammation and cell-mediated immune responses [5,6]. Changing the FA composition of cells involved in the inflammatory response influences their functions. The anti-inflammatory effects of omega-3 (n-3) polyunsaturated (PU) FAs suggest that they may be useful as therapeutic agents in disorders with an inflammatory component [7].

The n-3 PUFAs found in fish oil (FO), primarily EPA and DHA, compete with arachidonic acid (AA) (an n-6 PUFA) for use of the same enzymes, including cyclooxygenase and lipoxygenase [8,9]. Thus FO has anti-inflammatory potential by interfering with the AA pathway and by producing less inflammatory eicosanoids (e.g. prostaglandin E_3 (PGE_3), thromboxane A_3 (TXA_3) and leukotriene B_5 (LTB_5)) as well as inflammation resolving protectins, resolvins, and maresins. FO is also rich in the antioxidant α-tocopherol, which is added to prevent the oxidation of its constituent FAs [9,10]. Based on experimental and clinical studies, the most favourable n-6:n-3 PUFA intake ratio is proposed to range between 2:1 and 4:1 [11–14]. There is clinical data suggesting that n-3 PUFAs have beneficial effects on the immune system and organ function and improve clinical outcomes in surgical and acute respiratory distress syndrome (ARDS) patients. In addition, there is some promising data on their use in septic patients [6,14–16]. However, clinical data in the latter group of patients is sparse and inconsistent.

The aim of this study was to compare a four-oil lipid emulsion (LE) containing 30% soybean oil (SO), 30% medium-chain triglycerides (MCTs), 25% olive oil (OO) and 15% FO (SMOFlipid®), with a 100% SO-based LE in terms of the following outcomes: 1) plasma phospholipid FA composition, 2) inflammatory mediators in plasma, 3) routine biochemical parameters, 4) sequential organ failure assessment (SOFA) score and 5) clinical outcomes. The target population was patients with SIRS, with or without sepsis, or ARDS in the intensive care unit (ICU), requiring PN for more than 5 days. It was hypothesised that a four-oil LE including FO would increase plasma EPA, modify plasma total phospholipid fatty acid composition, decrease circulating inflammatory cytokine concentrations, and improve clinical outcomes.

2. Materials and methods

2.1. Study design

This study was a single-centre, double-blind, randomised controlled trial in ICU patients admitted to the ICU of Wits Donald Gordon Medical Centre (WDGMC) in Johannesburg, South Africa with documented SIRS or sepsis and ARDS.

2.2. Sample size

The total number of patients needed was determined to be at least 72 using plasma phospholipid FA composition as the primary outcome for the sample size calculation. This number was calculated using a power analysis for ANOVA with two groups, significance level of 0.05 and a small to medium effect size of 0.55. Sample size $n = 36$ in each group was expected to yield 90% power to detect this effect size.

2.3. Patient selection

A total number of 75 adult patients were included in the study; seven patients were excluded due to insufficient biochemical results, protocol violation or withdrawn consent, leaving a total of 68 patients. Thirty-five patients concluded the trial in the study group (SG) versus 33 patients in the control group (CG) (Fig. 1).

Adult patients diagnosed with SIRS or sepsis and/or ARDS who were predicted to need PN for more than 5 days were included

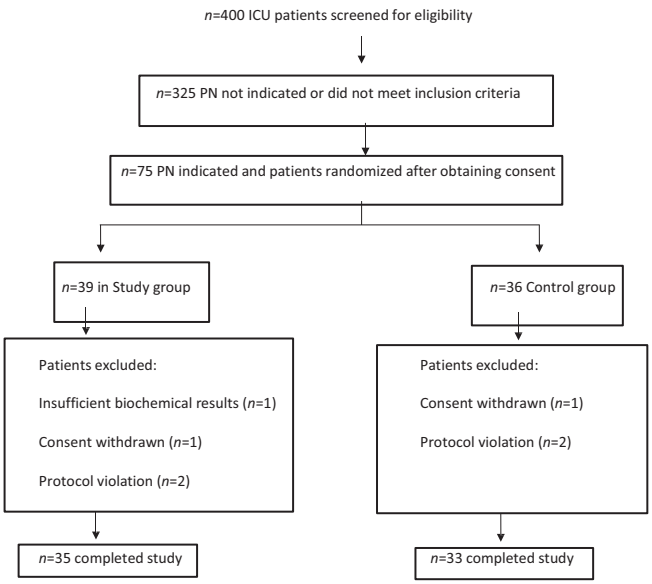

Fig. 1. Flow diagram of patient flow through the study.

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consecutively at the time of admission to the ICU. Patients were recruited between April 2015 and June 2016. Sepsis was defined as suspected or proven infection plus SIRS (defined as presence of pyrexia, tachycardia, tachypnoea and/or leukocytosis). Severe sepsis was defined as sepsis with organ dysfunction (hypotension, hypoxaemia, oliguria, metabolic acidosis and/or thrombocytopaenia). Septic shock was defined as severe sepsis with hypotension despite adequate fluid resuscitation [17,18].

The exclusion criteria were: <18 yr old, on full enteral feeding, pregnancy, treatment with immunosuppressive drugs or treatment with hydrocortisone >300 mg/day at admission, plasma triglycerides >4.52 mmol/l (>400 mg/dl), chronic liver disease or acute hepatitis, RIFLE stage III and IV renal failure, recent stroke and known allergic reaction to fish or egg proteins confirmed by previous medical history.

Once a patient was identified as eligible and consent was obtained, the dietitian calculated the acute physiology and chronic health evaluation (APACHE) II and SOFA scores, and nutritional assessment was performed. A PN prescription was then recommended to the clinician for finalisation after taking laboratory results into account. The dispensing pharmacist was responsible for randomising patients to either receive PN containing a four-oil LE including FO (SMOFlipid®: 30% LCT, 30% MCT, 25% OO, 15% FO, provided in a complete all-in-one PN bag by Fresenius Kabi: study group) or a SO-based lipid emulsion (Intralipid® 100% LCT, provided in a complete all-in-one PN bag by Fresenius Kabi: control group), according to a randomisation sheet.

The PN was started on the day after admission to the study. By following the above procedure there was no deviation from usual standardised PN prescription techniques, the only difference being the fat composition (Table 1). The decision to start enteral nutrition (EN) was based on an absence of contra-indications to EN and the resolution of post-operative gastrointestinal dysfunction. Patient information was recorded daily until discharge from ICU.

2.4. Anthropometric assessment

Weight and height were determined or estimated according to acknowledged procedures. Body Mass Index (BMI) was calculated on admission using recorded or estimated weight (kg)/height (m^2) and used to classify patients as undernourished, normal, overweight or obese [19,20].

Table 1
Composition of the treatment and control parenteral nutrition.

Component Per 1000 ml	Study group PN Code: ITN 8807	Control group PN Code: ITN 8007
Total energy (kcal/l)	929	929
Non-protein energy (NPE; kcal/l)	753	753
Carbohydrates (g/l)	84 (45% of NPE)	84 (45% of NPE)
Fat (g/l)	42 (55% of NPE)	42 (55% of NPE)
Soybean oil (g/l)	12.6	42.0
Medium chain triglycerides (g/l)	12.6	0.0
Olive oil (g/l)	10.5	0.0
Fish oil (g/l)	6.3	0.0
EPA + DHA (g/l)	1.9	0.0
n-6:n-3 fatty acid ratio	2.5:1	7:1
Nitrogen (g/l)	7	7
Glutamine (g/l)	6.3	6.3
Vitamins, minerals and trace elements	RDA	RDA
Osmolarity (mOsm/l)	981	978

NPE: non-protein energy; RDA: recommended daily allowance; EPA: eicosapentaenoic acid; DHA: docosahexaenoic acid.

2.5. Nutritional intervention

The American Society of Parenteral and Enteral Nutrition (ASPEN) and European Society of Clinical Nutrition and Metabolism (ESPEN) guidelines (25–30 kcal/kg/day total energy (TE) and protein 1.2–2 g/kg/day) were used to calculate energy and protein requirements [19,21]. Both groups of study participants received micronutrients, glutamine and electrolytes as part of the complete PN. The PN bags in the SG or CG were prescribed according to the study participants' nutritional and fluid requirements and the administration rate was adjusted accordingly (Table 1).

The commencement of enteral nutrition (EN) was not defined in the protocol and was started as soon as the treating physician and dietitian deemed it to be feasible according to consensus guidelines and hospital protocol. Decisions were made regarding the appropriate feeding options, either continue with full PN, or start trickle EN via a feeding tube and continue with PN or start introducing per os EN and continue with PN. The nutritional intake of EN and PN was calculated to avoid overfeeding.

2.6. Clinical outcomes

The SOFA score was calculated daily and days on mechanical ventilation, length of stay (LOS) and mortality were recorded.

2.7. Laboratory measurements

All blood samples were collected on admission, immediately prior to starting the PN (day 1), 24 h after initiating PN (day 2), 48 h after initiating PN (day 3) and five days after initiating PN (day 6). Routine biochemical assessments included full blood count (FBC), urea, creatinine and electrolytes, C-reactive protein (CRP), calcium, magnesium & phosphate, liver function tests (aspartate aminotransferase [AST], alanine aminotransferase [ALT], gamma-glutamyl transferase [GGT] and total bilirubin), triglycerides (TG), glucose and blood gases. Blood samples were collected at the same time each day via an arterial line and analysed on site. The blood required for plasma total phospholipid FAs and cytokines was collected on days 1, 3 and 6 at the same time as the routine bloods. These samples were centrifuged and plasma stored at −80 °C until analysed.

Routine biochemical measurements were taken as part of the monitoring protocol for patients on PN. Electrolytes were corrected according to patients' individual requirement. Glycaemic control was managed according to ICU protocol. Based on the laboratory measurements, the SOFA score was calculated daily.

2.8. Plasma total phospholipid fatty acid composition analysis

Total phospholipid FA composition analysis in plasma was performed within 18 months after collection and analysed according to previously described methodology [22]. FAs were analysed by gas chromatography tandem mass spectrometry (GCMSMS) on an Agilent Technologies 7890 A Gas Chromatograph system equipped with an Agilent Technologies 5975C VL mass selective detector (Agilent Technologies, Santa Clara, USA). The gas chromatography separation of fatty acid methyl esters (FAMEs) was carried out on a BPX 70 capillary column (60 m × 0.25 mm x 0.25 mm; SGE Analytical Science, Melbourne, Australia) by using helium as the carrier gas at a flow rate of 1.3 mL/min. Quantitation of FAMEs was performed by using the selected ion-extraction method on the basis of the response of two diagnostic ions. FAME peaks were identified and calibrated against a standard reference mixture of 33 FAMEs (Nu-Chek Prep, Waterville, USA) and two single FAME standards (Larodan Fine Chemicals AB, Solna, Sweden). Relative

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percentages of fatty acids were calculated by taking the concentration of a given fatty acid derivative as a percentage of the total concentration of all fatty acids identified in the sample.

2.9. Cytokine analysis

Cytokine (TNF-α, IL-1α, IL-6 & IL-10) concentrations in plasma were measured using MILLIPLEX® kits (Merck Millipore, Billerica, MA, USA) on the MAGPIX® instrument according to the Milliplex instructions. All samples were evaluated in duplicate by a single technician who was blinded to participant groups. All analyte levels in the quality-control reagents included in the kits were within the expected ranges. All median fluorescent intensity data were acquired using the Bio Plex MP™ software (Bio-Rad, Hercules, CA, USA) and analysed on the Bio Plex manager version 6.1 software (Bio-Rad) [23].

2.10. Statistical analysis

Statistical analyses were performed using STATISTICA version 13.2 (StatSoft Inc. (2016) STATISTICA (data analysis software system, www.statsoft.com).

Summary statistics were used to describe the variables. Distributions of variables were analysed with histograms and/or frequency tables. Medians or means were used as the measures of central location for ordinal and continuous responses and standard deviations or quartiles as indicators of spread.

Evaluations of the results of the nutritional intake, laboratory parameters, total plasma phospholipid FAs, cytokines, PaO_2/FiO_2 ratio and clinical data were performed by descriptive statistical analysis for each variable and at day 1, day 3 and day 6. Baseline was defined as the data obtained before the intervention. Endpoints were defined as net change of post intervention from baseline.

The relationships between nutritional intake, TG, liver enzymes, PaO_2/FiO_2 ratio, cytokines, fatty acid composition SOFA score, ICU mortality and nutritional efficacy and type of PN were analysed using appropriate analysis of variance (ANOVA) and appropriate repeated measures analysis of variance (RMANOVA), when responses were measured at day 1, day 3 and day 6.

For completely randomised designs when residuals of the above analyses were not normally distributed, the Mann–Whitney test or the Kruskal–Wallis test was used and for repeated measures designs the Wilcoxon or Friedman tests were used.

The relationship between two continuous variables was analysed with regression analysis and the strength of the relationship measured with Pearson's correlation coefficient or Spearman's correlation coefficient if the continuous variables were not normally distributed or if the input was ordinal. The relation between nominal variables was investigated with contingency tables and appropriate chi-square tests, namely the likelihood ratio chi-square test or McNemar's test.

A p-value of $p < 0.05$ represented statistical significance in hypothesis testing and 95% confidence intervals were used to describe the estimation of unknown parameters.

2.11. Ethics and legal aspects

The study was approved by the Health Research Ethics Committee of Stellenbosch University (M12/10/052) and the Human Research Ethics Committee (Medical) of the University of Witwatersrand (M14111090). Permission was granted by the director of the ICU and the hospital manager at WDGMC. Consent was obtained from the study participant or his/her closest relatives. The study was conducted in accordance with the Helsinki Declaration and was registered on the South African National Clinical Trials Register database, registration number: DOH-27-0616-4323.

3. Results

A total number of 75 patients were included in the study; however after the exclusion of seven patients, a total of 68 patients remained. Thirty-five patients concluded in the study group (SG) versus 33 patients in the control group (CG) (Fig. 1). Patients were followed up for 5 days after PN was commenced. On admission to the study the baseline characteristics of the patients in the two treatment groups did not differ (Table 1 Supplementary appendix). The gender distribution was 66% male and 34% female in the SG vs 56% male and 45% female in the CG ($p = 0.334$). The average age was 60.8 ± 13.9 years in SG vs 55.7 ± 14.8 in CG. The majority of the participants were surgical admissions (85% in SG vs 91% in CG) and the remainder were medical admissions.

3.1. Nutritional intakes

Total energy, protein, fat, carbohydrates and glutamine intakes did not differ between the groups throughout the study period (Table 2). The SG received FO ranging between 0.09 ± 0.03 g/kg/day (minimum) and 0.22 ± 0.11 g/kg/day (maximum), providing between 1.15 ± 0.44 g to 2.37 ± 0.79 g EPA and 1.72 ± 0.42 g to 2.18 ± 0.44 g DHA per day. The total FO intake ranged from 7.2 ± 2.7 to 15 ± 2.7 g/day. The phytosterol intake was significantly more in the CG ($p = 0.008$) and α-tocopherol intake was significantly more in the SG ($p<0.001$) over the entire study period. Enteral nutrition was started on day 4.0 ± 2.1 in the SG versus day 3.6 ± 1.9 in CG ($p = 0.420$). Nutritional intake from supplemental EN and oral intake were not accurately documented. Thus, the nutrient intake tabulated on day 6 was less than that of day 3, as it only included intake from PN. Table 2 only includes nutritional intake from PN.

Only 63% of patients in the SG and 54% in the CG received PN for the full 6 days, and the cumulative FO intake was significantly more in the SG patients that received PN for 6 days compared with those who received PN for fewer days ($p = 0.032$).

3.2. Laboratory measurements

There were no differences between the treatment groups in white cell count (WCC), blood glucose, triglycerides, liver enzymes and total bilirubin (Table 3). Even though triglycerides increased significantly in both groups, the increase was significantly less in the SG ($p = 0.035$).

AST, ALT and bilirubin improved in both groups (Table 3). There was a decrease in AST, ALT and a trend towards a decrease in bilirubin levels from day 1 to day 6 in the SG. There was no statistical difference in the PaO_2/FiO_2 ratio between the two groups (Table 3).

3.3. Plasma C-reactive protein and cytokine concentrations

Plasma CRP and cytokine concentrations did not differ significantly between the two groups prior to initiation of PN and throughout the study period. Concentrations of TNF-α decreased from day 1 to day 6 in the SG, whereas they increased in the CG, but the difference was not statistically significant (Table 2 Supplementary appendix).

3.4. Plasma total phospholipid fatty acids composition

The five-day infusion of a four-oil LE in the SG providing 0.09–0.22 g FO/kg/day resulted in multiple changes in the plasma total phospholipid FA composition (Table 4). Baseline plasma FA

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Table 2
Nutritional intake from parenteral nutrition according to group and day.

	Study Group ($n = 35$)			Control Group ($n = 33$)			Intervention effect[a]
	Day 1	Day 3	Day 6	Day 1	Day 3	Day 6	p value
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
Energy (kcal)	1130.8 ± 429.3	2249.9 ± 386.1	1132.5 ± 1034.5	1034.0 ± 430.2	2222.6 ± 352.4	1176.1 ± 984.7	$p = 0.357$[b] $p = 0.758$[c] $p = 0.858$[d]
Protein (g/kg)	0.67 ± 0.26	1.33 ± 0.16	0.68 ± 0.64	0.65 ± 0.25	1.39 ± 0.2	0.70 ± 0.61	$p = 0.740$[b] $p = 0.157$[c] $p = 0.914$[d]
Glutamine (g/kg)	0.09 ± 0.03	0.18 ± 0.03	0.09 ± 0.1	0.09 ± 0.03	0.2 ± 0.07	0.09 ± 0.09	$p = 0.873$[b] $p = 0.230$[c] $p = 0.862$[d]
Fat (g/kg)	0.63 ± 0.24	1.26 ± 0.16	0.65 ± 0.59	0.62 ± 0.24	1.32 ± 0.19	0.66 ± 0.57	$p = 0.892$[b] $p = 0.188$[c] $p = 0.877$[d]
Carbohydrate (g/kg)	1.36 ± 0.61	2.58 ± 0.34	1.34 ± 1.27	1.3 ± 0.62	2.80 ± 0.59	1.47 ± 1.27	$p = 0.675$[b] $p = 0.050$[c] $p = 0.651$[d]
Phytosterol (mg)	48.8 ± 18.3	102.4 ± 20.2	52.2 ± 45.4	96.2 ± 33.4	205.9 ± 34.2	99.8 ± 92.8	$p<0.001$[b] $p<0.001$[c] $p = 0.009$[d]
α-tocopherol (mg)	48.0 ± 17.7	100.0 ± 17.9	50.9 ± 45.6	9.9 ± 8.7	18.5 ± 3.1	8.9 ± 8.3	$p<0.001$[b] $p<0.001$[c] $p<0.001$[d]
Fish oil (g)	7.2 ± 2.7	15.0 ± 2.7	11.2 ± 4.8				
Fish oil (g/kg)	0.09 ± 0.03	0.19 ± 0.03	0.14 ± 0.06				
EPA (g)	1.15 ± 0.44	2.372 ± 0.47	1.75 ± 0.79				
DHA (g)	1.72 ± 0.42	2.18 ± 0.44	1.61 ± 0.72				

[a] Differences between the study group and control group at each time point were examined. EPA: eicosapentaenoic acid; DHA: docosahexaenoic acid.
[b] Difference between groups on day 1.
[c] Difference between groups on day 3.
[d] Difference between groups on day 6.

Table 3
Routine biochemical measurements according to group and day.

Measurement	Study Group (n = 35)			Control Group (n = 33)			Intervention effect[a]
	Day 1	Day 3	Day 6	Day 1	Day 3	Day 6	P value
	Mean ± SE	Mean ± SE	Mean ± SE	Mean ± SD	Mean ± SE	Mean ± SE	
TG (mmol/L)	1.47 ± 0.11	1.78 ± 0.17	1.99 ± 0.19	1.44 ± 0.11	2.27 ± 0.17	2.17 ± 0.18	p = 0.035
AST (IU/L)	73.36 ± 15.73	35.30 ± 4.35	35.90 ± 5.01	53.90 ± 16.23	33.13 ± 4.49	38.84 ± 5.17	P = 0.377
ALT (IU/L)	45.84 ± 9.23	32.90 ± 8.18	20.13 ± 2.53	28.9 ± 9.38	26.83 ± 8.31	17.7 ± 2.58	p = 0.377
GGT (IU/L)	76.79 ± 18.01	68.89 ± 12.38	126.96 ± 23.39	75.86 ± 17.7	67.35 ± 12.17	150.41 ± 22.98	p = 0.571
Bilirubin (mmol/L)	12.5 ± 3.39	8.64 ± 1.83	9.22 ± 2.05	19.58 ± 3.25	11.54 ± 1.75	16.08 ± 1.97	p = 0.228
PaO_2/FiO_2 ratio	285.79 ± 25.39	228.51 ± 22.51	254.02 ± 25.01	319.3 ± 29.5	293.25 ± 26.15	305 ± 29.07	p = 0.769
WCC (10^9 cells/L)	14.16 ± 1.97	12.1 ± 1.39	14.84 ± 1.67	17.85 ± 2.03	14.24 ± 1.44	14.99 ± 1.73	p = 0.37
Glucose (mmol/L)	7.44 ± 0.33	8.44 ± 0.35	7.75 ± 0.48	6.79 ± 0.35	8.54 ± 0.36	7.92 ± 0.5	p = 0.483

[a] Differences between the study group and control group over the 6 days were examined. TG: triglyceride; AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: gamma-glutamyl transferase; PaO_2/FiO_2: partial pressure arterial oxygen to fractional inspired oxygen; WCC: white cell count.

compositions were similar between the two treatment groups except for lower linoleic acid (LA, $p = 0.008$) and higher arachidonic acid (AA, $p = 0.005$) levels in the SG.

Oleic acid (OA) composition increased from day 1 to day 3 in both groups, and then remained constant until day 6. OA was higher in the SG than in the CG on day 6 ($p = 0.022$, Table 4 and Fig. 2A). The percentage of LA increased from day 1 to day 3 in the CG and then remained constant. LA decreased in the SG (17.34 ± 3.37 on day 1–15.05 ± 2.14 on day 6). Linoleic acid was significantly lower in the SG compared to the CG throughout the study period (Table 4 and Fig. 2B).

Alpha linolenic acid (ALA) increased significantly in both groups ($p = 0.004$); however ALA was lower in the SG at day 3 and 6 (both $p < 0.001$) than in the CG (Fig. 2C). AA decreased in both groups, the decrease in the SG occurred throughout the study period, whereas the decrease in the CG occurred between day 1 and day 3 and then remained constant until day 6. Compared to the CG, overall AA was reduced in the SG ($p = 0.005$) (Fig. 2D).

Myristic acid (MA) levels were similar in both groups at baseline. The levels increased in the SG from day 1 to day 6 and only increased in the CG from day 3 to day 6. On day 3 the MA levels were significantly different ($p = 0.003$) in both groups; however on day 6 ($p = 0.054$) the difference was no longer significant.

Plasma EPA increased significantly in the SG: the biggest increase was from day 1 to day 3 and it continued to increase up to day 6 (Fig. 2E). DHA remained constant in the SG and increased slightly after day 3 but decreased in the CG. Both EPA and DHA were increased by the four-oil LE treatment (both $p<0.001$) (Fig. 2F).

The plasma n-6 PUFA:n-3 PUFA ratio at baseline was similar between the two groups. This ratio decreased in the SG (5.61 ± 1.8 day 1–2.84 ± 0.73 day 6) and remained constant in the CG

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Table 4
Plasma total phospholipid fatty acid composition (% of total fatty acids) according to group and day.

	Study Group (n = 29)			Control Group (n = 30)			Intervention effect[a]
	Day 1	Day 3	Day 6	Day 1	Day 3	Day 6	*p* value
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
Oleic acid	9.71 ± 2.25	11.95 ± 2.33	11.89 ± 2.51	9.70 ± 1.83	10.94 ± 2.08	10.44 ± 2.03	$p = 0.980$[b] $p = 0.086$[c] $p = 0.022$[d]
Linoleic acid	17.34 ± 3.37	16.28 ± 2.63	15.05 ± 2.14	19.7 ± 3.22	21.47 ± 3.87	20.66 ± 3.15	$p = 0.008$[b] $p<0.001$[c] $p<0.001$[d]
Alpha linolenic acid	0.09 ± 0.06	0.15 ± 0.07	0.18 ± 0.09	0.12 ± 0.13	0.29 ± 0.15	0.34 ± 0.21	$p = 0.243$[b] $p < 0.001$[c] $p < 0.001$[d]
Arachidonic acid	14.78 ± 3.16	12.55 ± 2.09	11.28 ± 1.59	13.25 ± 2.61	11.47 ± 2.9	11.64 ± 2.57	$p = 0.048$[b] $p = 0.108$[c] $p = 0.053$[d]
Eicosapentaenoic acid	0.66 ± 0.56	2.07 ± 0.77	3.42 ± 0.95	0.55 ± 0.35	0.54 ± 0.42	0.94 ± 0.8	$p = 0.360$[b] $p<0.001$[c] $p<0.001$[d]
Docosahexaenoic acid	5.11 ± 1.58	5.09 ± 1.16	5.86 ± 1.19	4.4 ± 1.38	4.07 ± 1.19	3.74 ± 1.31	$p = 0.071$[b] $p = 0.017$[c] $p<0.001$[d]
n-6:n-3 fatty acid ratio	5.61 ± 1.80	4.03 ± 0.97	2.84 ± 0.73	6.38 ± 2.10	6.67 ± 1.79	6.52 ± 1.81	$p = 0.137$ $p<0.001$[c] $p<0.001$[d]

[a] Differences between the study group and control group at each time point were examined.
[b] Difference between groups on day 1.
[c] Difference between groups on day 3.
[d] Difference between groups on day 6.

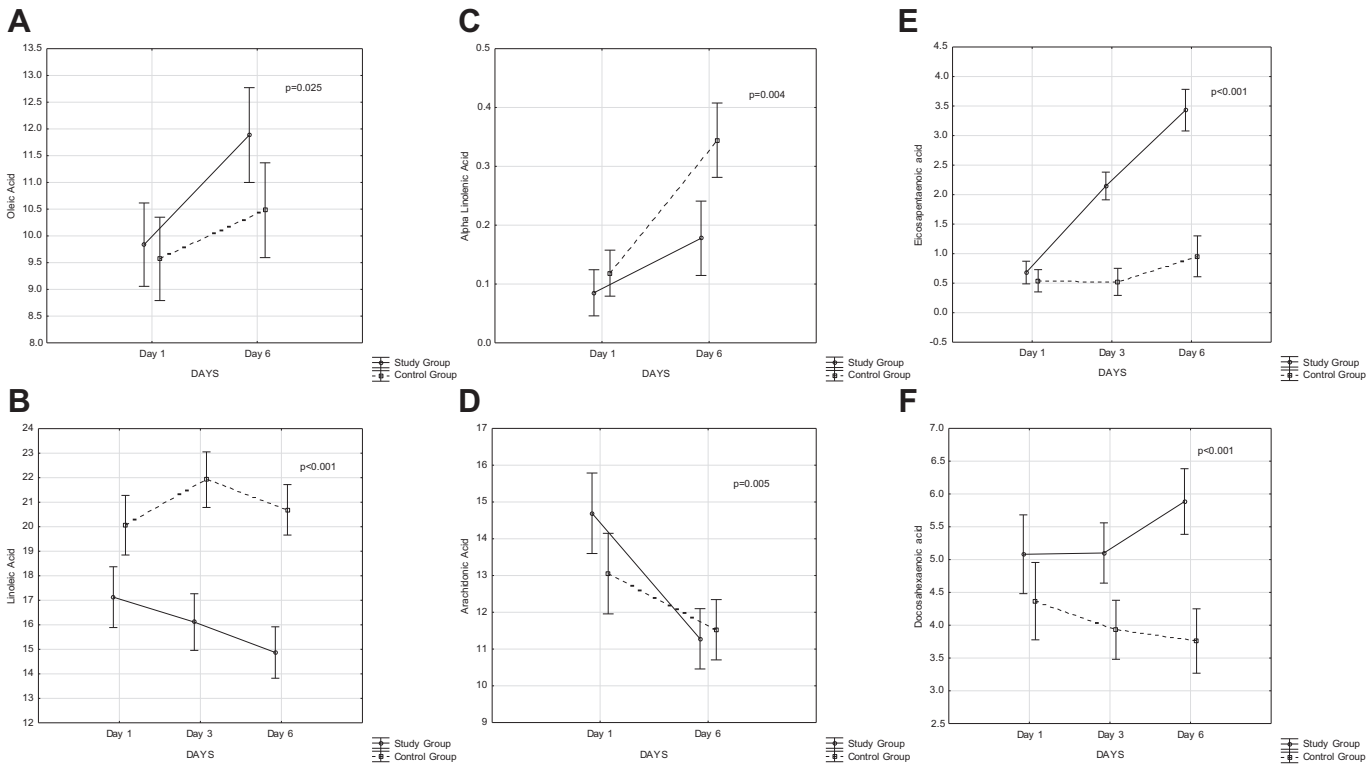

Fig. 2. Plasma total phospholipid fatty acid composition (% of total fatty acids) per group over the study period. 2(A) Oleic acid; 2(B) Linoleic acid; 2(C) Alpha linoleic acid; 2(D) Arachidonic acid; 2(E)Eicosapentaenoic acid; 2(F) Docosahexanoic acid.

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(6.38 ± 2.1 day 1–6.52 ± 1.81 day 6). The n-6 PUFA:n-3 PUFA ratio was reduced by the four-oil LE (p=<0.001, Table 4).

3.5. Clinical outcomes

CRP levels decreased in both groups during the intervention period. Days on mechanical ventilation (1.24 ± 0.83 days in SG versus 0.88 ± 1.63 days in CG, $p = 0.385$) and length of stay (LOS) in the ICU (9.5 ± 7.09 days in SG versus 10.7 ± 7.6 days in CG, $p = 0.490$) were not different between the two groups. The SOFA score improved in both treatment groups during the intervention (Table 5). A medium negative correlation between day 3 EPA intake and day 3 SOFA score ($r = -0.405$, $p = 0.018$) was noted. Even though the mean baseline APACHE II score was higher in the SG ($p = 0.190$), there was no difference in mortality ($p = 0.240$).

4. Discussion

This study compared a four-oil LE containing FO (SMOFlipid®) with a 100% SO-based LE in critically ill adult ICU patients. The baseline characteristics of the patients did not differ between the two groups, nor did the nutritional intakes differ, except the SG received FO, providing EPA and DHA, a significantly higher amount of α-tocopherol and a significantly lower amount of phytosterols. There is evidence that administration of large doses of phytosterols can cause cholestasis and parenteral nutrition-associated liver disease (PNALD) [14]. This study showed a non-significant reduction in liver enzymes, particularly AST, ALT and bilirubin in the SG.

EN was started on day 4 in the SG versus day 3.6 in the CG and only 63.2% of participants in the SG and 54.5% in CG received PN for the full six days. The maximum intake of FO, EPA and DHA was on day 3. This maximum intake of EPA was associated with a significant improvement in SOFA score.

To our knowledge this is the first randomised controlled study using SMOFlipid® in septic ICU participants, although it has been studied previously in post-surgery participants [24–31]. In these studies SMOFlipid® was found to decrease the concentrations of inflammatory cytokines and eicosanoids [25,31], decrease liver enzymes [24,26,28], increase plasma α-tocopherol [24,25] and reduce length of hospital stay [25]. Other FO containing LEs have also been studied in post-surgical patients and were associated with decreased production of inflammatory eicosanoids and cytokines [32–34], improved immune function, reduced liver enzymes [33,35] and improved clinical outcomes [34–39].

These other FO containing LEs have also been studied in critically ill and septic participants [40–44]. In some of these studies the use of FO containing LEs was associated with decreased inflammatory markers, improved respiratory function [40], significant reduction in nosocomial infections and prolonged predicted time free of infection [43]. Heller et al. [45] used a FO supplement in a heterogeneous group of participants and identified a dose-dependent (0.1–0.2 g/kg) reduction in mortality, infection rate and length of stay. Grau-Carmona et al. showed a non-significant shorter length of mechanical ventilation and hospital stay in patients receiving FO [43]. However, other studies reported no effect on mortality or length of stay [3,42].

The dose of fish oil administered in this study ranged between 0.09 and 0.22 g/kg and is consistent with the dose that other studies found to be clinically favourable [43,45,46]. The highest dose of FO was on day 3 as EN was started afterwards and resulted in a reduction in intake of PN and FO.

Plasma cytokine levels did not differ significantly between the two groups; however plasma levels of TNF-α decreased in the SG and increased in the CG. Similar results were shown in surgical participants with a FO supplement and SO versus SO alone [34,47], and FO supplement plus MCT/LCT versus MCT/LCT alone [32]. Kreymann et al. found no clear-cut effect on TNF-α levels when using FO admixtures and FO-supplemented LEs [48].

This study demonstrated a significant increase in OA and ALA in both groups. Plasma EPA increased significantly in the SG, whereas DHA increased after day 3. DHA levels decreased significantly in the CG. AA decreased in both groups, however the decrease was more in the SG. Similar results were seen using the same LE in surgical patients. Grimm et al. demonstrated an increase in n-3 PUFAs, EPA and DHA, and a decrease in LA, AA and total n-6 PUFAs after 6 days [25].

Other FO containing LEs studied in critically ill and septic patients showed similar results with regards to EPA. In the study by Barbosa et al., the use of a FO containing LE was associated with increases in plasma EPA, but there were no differences in DHA and AA concentrations [40]. Mayer et al. demonstrated a marked increase in EPA and DHA concentrations in patients receiving FO-based infusions. The levels plateaued after 7 days; the sum of EPA and DHA surpassed the AA level nearly twofold [49]. However, the doses of FO, EPA and DHA used by Mayer et al. were higher than used here.

The optimal ratio of n-6:n-3 PUFAs has been questioned and whether the provision of an LE with an optimum ratio would be associated with metabolic and clinical benefits. Based on previous studies, a ratio between 2:1 and 4:1 can be considered as beneficial to severely ill patients [11–14]. SMOFlipid® was developed to have an optimal n-6:n-3 PUFAs ratio of 2.5:1. In this study, the plasma n-6:n-3 PUFAs ratio decreased significantly in the SG, whereas it remained constant in the CG. The plasma ratio on day 6 in the SG was similar to the values recommended for LEs [39]. Similar results were also seen in surgical patients where the ratio n-6:n-3 PUFAs was profoundly reduced and leukotriene B_5 release from n-3 PUFAs was enhanced on day 6, whereas the release of leukotriene B_4 from n-6 PUFAs was lowered with SMOFlipid® [25].

In terms of clinical outcomes, this study showed an improvement in CRP levels in both groups. Days on mechanical ventilation, LOS in the ICU and mortality were not different between the groups. SOFA score also improved in both groups, a significant negative correlation was found between EPA intake on day 3 and

Table 5
Clinical outcome measurements according to group and day.

	Study Group (n = 35)						Control Group (n = 33)						Intervention effect[a]
	Day 1			Day 6			Day 1			Day 6			
	Mean ± SE	−95% LCL	+95% UCL	Mean ± SE	−95% LCL	+95% UCL	Mean ± SE	−95% LCL	+95% UCL	Mean ± SE	−95% LCL	+95% UCL	p value
SOFA	5.77 ± 0.75	4.26	7.28	4.27 ± 0.77	2.72	5.82	5.91 ± 0.86	4.191	7.635	3.83 ± 0.88	2.06	5.6	$p = 0.578$
CRP (mg/L)	199.82 ± 23	153.74	245.9	103.6 ± 13.9	75.71	131.46	215.47 ± 23.4	168.56	262.37	116.99 ± 14.16	88.62	145.36	$p = 0.951$
TNF-α (pg/ml)	9.45 ± 2.53	4.38	14.52	5.09 ± 3.12	−1.16	11.34	4.95 ± 2.49	−0.03	9.93	8.59 ± 3.06	2.44	14.73	$p = 0.122$

[a] Differences between the study group and control group were examined. SOFA: Sequential Organ Failure Assessment; CRP: c-reactive protein; TNF-α: tumour necrosis factor – alpha; LCL: lower confidence limit; UCL: upper confidence limit.

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the SOFA score. Grimm et al. demonstrated a significantly reduced length of hospital stay (13.4 ± 2.0 vs 20.4 ± 10 days) with FO LE in surgical patients [25]. Heller et al. demonstrated a reduction in ICU LOS when the n-6:n-3 PUFAs ratio was 2:1 [39].

A secondary analysis of data comparing the effects of different IV LEs showed that patients receiving SO, compared with patients receiving either olive or fish oil, had a longer time to termination of mechanical ventilation and ICU discharge alive [41]. Grecu et al. showed significant reduction in reoperation rates, ICU and hospital LOS, but no difference in mortality, with a FO containing LE in critically ill patients [50]. Another study using the same FO LE showed a significant decrease in new organ dysfunction, but no significant decrease in LOS [46]. Other FO-containing LE studies reported no effect on length of stay [3,40,42,51], days of mechanical ventilation [40,42,49,51] and mortality [3,40,42,49,51].

A recent meta-analysis confirmed a significant reduction in infection rates by 35% in critically ill patients with no overall effect on ICU LOS. They concluded that FO admixtures and supplemental FO LEs are advantageous for the majority of patients compared with LCT or MCT/LCT LEs because of their balancing n-3 FA content [48]. However, a recent review found insufficient high-quality data investigating the true effect of PN with FO containing LEs compared with other IVLEs on clinical outcomes [52].

It is difficult to compare the results of this study with other FO LE studies owing to the different dose of FO and duration of treatment.

The limitations of this study are that only half the patients received PN for 6 days; this affected the duration as well as the dose of FO over the study period. There was a definite signal that the intake of EPA and FO on day 3 showed a beneficial effect. It was not possible to determine the full nutritional intake throughout the study period owing to the incomplete recording of EN intake. Infection rate, as well as days on antibiotics, was also not documented and would have provided valuable information about clinical outcomes. The study population may have been somewhat heterogenous as to the causes and severity of SIRS and ARDS. Finally, we were unable to test plasma α-tocopherol levels, which would have been an interesting additional result as the administration was significantly different between the two groups.

5. Conclusion

PN containing a four-oil LE with FO at a dose of 0.09–0.22 g/kg in critically ill adult ICU patients increased plasma EPA and DHA, and decreased n-6:n-3 PUFA ratio. It appeared to be safe and well tolerated. The negative relationship of EPA intake with SOFA seems promising, but EPA intake and effects may have been diluted by enteral nutrition started in more than half of patients on day 4. There was no significant difference in terms of biochemical measurements, SOFA score, length of ICU stay and mortality. More research is needed in this patient population, particularly regarding dose, duration and timing of FO, EPA and n-6:n-3 PUFA ratio and their effects on clinical outcomes.

Statement of authorship

VD, RB and MGLS were involved in the conception and design of the study. VD was responsible for the acquisition and collation of data and DGN for the statistical analyses. All authors contributed to the interpretation of data, drafting the article and revising it critically for important intellectual content.

Conflict of Interest Statement and Funding Sources

V. Donoghue: Study was conducted in personal capacity for Masters degree; employed by Fresenius Kabi South Africa. G.K. Schleicher: No conflicts declared. M.G.L. Spruyt: Advisory Board Member for Fresenius Kabi South Africa. L. Malan: No conflicts declared. D.G. Nel: No conflicts declared. P.C. Calder: Has received writing and speaking fees from Fresenius Kabi Deutschland. R. Blaauw: Advisory Board Member for Fresenius Kabi South Africa, has received an unconditional research grant from Fresenius Kabi Deutschland. A partial, unconditional research grant for this study was received from Fresenius Kabi South Africa.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2018.12.010.

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